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**Blatt 2 der Bescheinigung**  
**Sheet 2 of the certificate**  
**Page 2 de l'attestation**

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A method for stimulating the immune system

Two different approaches have been used in the prior art to enhance the immune response against neoplastic cells. One approach uses the addition of cytokines like interleukin-2 (IL-2) or transfection of tumor cells and/or immune cells with genes coding for cytokines like IL-2 or other proteins enhancing the immune response like transfection of tumor cells with lymphotactin or like transfection of T-lymphocytes with CD-40 Ligand.

The second approach uses the inhibition of immunosuppressive molecules to enhance the body's immune response to tumor cells. Thus, J. NEUROSURG. 78 (1993) 944-51, Jachimczak et al. (1993) and WO 94/25588, Schlingensiepen et al. (1994) teach the use of antisense oligonucleotides targeted to TGF- $\beta$  to reverse tumor-induced immunosuppression.

Several documents in the prior art teach that a combination of these two approaches is either not efficacious or is not beneficial over use of one of the two approaches used alone.

Thus, CANCER BROTH. 8(2), 1993, 159 - 170, Gridley et al., as well as CANCER BROTH. 9(4), 1994, 317 - 327, Mao et al., both teach that a combination of anti-transforming growth factor-beta antibody with IL-2 does not cause significant antitumor effects.

Furthermore, PROC. NAT'L. ACAD. SCI 93, (1996), 2909-2914, Fakhrai et al., teaches that a combination of transfection with genes encoding antisense sequences to transforming growth factor beta (TGF- $\beta$ ) TGF- $\beta$  mRNA with transfection of IL-2 into tumor cells does not increase the immune response against the tumor compared to transfection with TGF- $\beta$  antisense alone.

Surprisingly, in contrast, we find that a combination of antisense oligonucleotides against TGF- $\beta$  with immunostimulatory molecules is more efficacious than either approach alone.

The present invention describes a method for enhancing the immune response including the immune response against tumor cells and/or cells containing viral antigens and/or cells expressing mutated antigens and/or cells involved in a pathological process, comprising the steps of

a) inhibiting the synthesis and/or function of molecules suppressing and/or downregulating and/or negatively affecting the immune response

combined with

b) applying and/or enhancing the synthesis and/or function of molecules stimulating and/or enhancing and/or upregulating and/or positively regulating the immune response

The present invention also describes combinations of molecules capable of enhancing the immune response against tumor cells and/or cells containing viral antigens and/or cells expressing mutated antigens and/or cells involved in a pathological process, comprising the steps of

a) inhibiting the synthesis and/or function of molecules suppressing and/or downregulating and/or negatively affecting the immune response

and

b) enhancing the synthesis and/or function of molecules stimulating and/or enhancing and/or upregulating and/or positively regulating the immune response

In a preferred embodiment of the invention a single molecule is capable of enhancing the immune response against tumor cells and/or cells containing viral antigens and/or cells expressing mutated antigens and/or cells involved in a pathological process, by

- a) inhibiting the synthesis and/or function of molecules suppressing and/or downregulating and/or negatively affecting the immune response
- and
- b) enhancing the synthesis and/or function of molecules stimulating and/or enhancing and/or upregulating and/or positively regulating the immune response

In a further preferred embodiment of the invention the single molecule capable of enhancing the immune response against tumor cells and/or cells containing viral antigens and/or cells expressing mutated antigens and/or cells involved in a pathological process, by

- a) inhibiting the synthesis and/or function of molecules suppressing and/or downregulating and/or negatively affecting the immune response
- and
- b) enhancing the synthesis and/or function of molecules stimulating and/or enhancing and/or upregulating and/or positively regulating the immune response

is a nucleic acid molecule

- coding for and/or containing antisense sequences and/or ribozymes capable of inhibiting immunosuppressive molecules including TGF- $\beta$ 1, TGF- $\beta$ 2, TGF- $\beta$ 3, IL-10 and/or PGE2-Receptor as well as
- coding for molecules including proteins and/or peptides stimulating and/or enhancing and/or upregulating and/or positively regulating the immune response.

In a further preferred embodiment of the invention the single molecule capable of enhancing the immune response is a nucleic acid molecule coding for

- sequences downregulating immunosuppressive molecules as well as
- sequences coding for molecules including proteins and/or peptides stimulating and/or enhancing and/or upregulating and/or positively regulating the immune response, these molecules including
  - a) Chemokines, including lymphotactin and/or immune cell attracting and/or
  - b) viruses and/or parts of viruses, including adenoviruses, papillomaviruses, Epstein-Barr-Viruses, Viruses that are non-pathogenic including Newcastle-Disease virus, Cow-pox-virus and/or
  - c) autologous and/or heterologous MHC-Molecules and/or
  - d) molecules involved in antigen processing and/or
  - e) molecules involved in antigen presentation and/or
  - f) molecules involved in mediating immune cell effects and/or

- g) molecules involved in mediating immune cell cytotoxic effects and/or
- h) molecules involved in antigen transportation and/or
- i) co-stimulatory molecules
- j) peptides enhancing recognition by immune cell and/or cytotoxic effects of immune cells
- k) the peptides containing one or more amino acids differing between a protein in the target cell from the other cell within an organism
- l) the peptides according to j) being
  - \*Peptides containing one or more mutations and/or amino acid substitutions of the ras protein amino and/or
  - \*Peptides containing one or more mutations and/or amino acid substitutions of the p53 protein and/or
  - \*Peptides containing one or more mutations and/or amino acid substitutions of the EGF-Receptor protein and/or
  - \*Peptides containing one or more mutations and/or amino acid substitutions of fusion peptides and/or fusion proteins and/or
  - \*Peptides containing one or more mutations and/or amino acid substitutions and/or amino acid substitutions caused by gene rearrangements and/or gene translocations and/or
  - \*Peptides containing one or more mutations and/or amino acid substitutions of the retinoblastoma protein and/or
  - \*Peptides containing one or more mutations and/or amino acid substitutions of proteins coded by oncogenes and/or protooncogenes and/or
  - \*Peptides containing one or more mutations and/or amino acid substitutions of proteins coded by anti-oncogenes and/or tumor suppressor genes and/or
  - \*Peptides derived from proteins differing in the target cell by one or amino acids from the proteins expressed by other cells in the same organism and/or
  - \*Peptides derived from viral antigens and/or coded by viral nucleic acids and/or
- m) tumor cell extracts and/or tumor cell lysates and/or adjuvants.

In a further preferred embodiment of the invention the single molecule capable of enhancing the immune response against tumor cells and/or cells containing viral antigens and/or cells expressing mutated antigens and/or cells involved in a pathological process, by

- a) inhibiting the synthesis and/or function of molecules suppressing and/or downregulating and/or negatively affecting the immune response
- and
- b) enhancing the synthesis and/or function of molecules stimulating and/or enhancing and/or upregulating and/or positively regulating the immune response

is a nucleic acid molecule coding for and/or containing antisense sequences and/or ribozymes capable of inhibiting immunosuppressive molecules including TGF- $\beta$ 1, TGF- $\beta$ 2, TGF- $\beta$ 3, IL-10 and/or PGE2-Receptor as well as sequences coding for IL-2 and/or IL-12 and/or IL-18 and/or an antigen present in tumor cells or pathogens, but not in normal cells and/or viral antigens.

In a preferred embodiment of the invention the nucleic acid molecules contain flanking sequences and/or vector sequences and/or sequences enhancing the expression and/or transfection of the nucleic acid molecules.

In a further preferred embodiment of the invention the nucleic acid molecules are part of one or more vectors and/or viral sequences and/or viral vectors.

In a preferred embodiment of the invention the oligonucleotides and/or ribozymes and/or nucleic acids have modifications at the bases, the sugars and/or the phosphate moieties of the oligonucleotides.

In a further preferred embodiment of the invention the oligonucleotides and/or ribozymes and/or nucleic acids have modifications wherein the modifications are phosphorothioate (S-ODN) internucleotide linkages and/or methylphosphonate internucleotide linkages and/or phosphoramidate linkages and/or peptide linkages and/or 2'-methoxyethoxy modifications of the sugar and/or modifications of the bases.

In a further preferred embodiment of the invention the oligonucleotides and/or ribozymes and/or nucleic acids are coupled to or mixed with folic acid, hormones, steroid hormones such as oestrogene, progesterone, corticosteroids, mineral corticoids, peptides, proteoglycans, glycolipids, phospholipids and derivatives therefrom.

The present invention also describes the combination of

1. Antisense nucleic acids, including ribozymes or derivatives thereof, transfected and/or directly applied as oligonucleotides capable of inhibiting expression and/or function of TGF- $\beta$ 1, TGF- $\beta$ 2, TGF- $\beta$ 3, IL-10 and/or PGE2-Receptor

with

**II. Enhancing expression in target cells and/or target pathogens of**

- a) Chemokines, including lymphotactin and/or immune cell attracting and/or
- b) viruses and/or parts of viruses, including adenoviruses, papillomaviruses, Epstein-barr-Viruses, Viruses that are non-pathogenic including Newcastle-Disease virus, Cow-pox-virus and/or
- c) autologous and/or heterologous MHC-Molecules and/or
- d) molecules involved in antigen processing and/or
- e) molecules involved in antigen presentation and/or
- f) molecules involved in mediating immune cell effects and/or
- g) molecules involved in mediating immune cell cytotoxic effects and/or
- h) molecules involved in antigen transportation and/or
- i) co-stimulatory molecules
- j) peptides enhancing recognition by immune cell and/or cytotoxic effects of immune cells
- k) the peptides containing one or more amino acids differing between a protein in the target cell from the other cell within an organism
- l) the peptides according to j) being
  - \*Peptides containing one or more mutations and/or amino acid substitutions of the ras protein amino and/or
  - \*Peptides containing one or more mutations and/or amino acid substitutions of the p53 protein and/or
  - \*Peptides containing one or more mutations and/or amino acid substitutions of the EGF-Receptor protein and/or
  - \*Peptides containing one or more mutations and/or amino acid substitutions of fusion peptides and/or fusion proteins and/or
  - \*Peptides containing one or more mutations and/or amino acid substitutions and/or amino acid substitutions caused by gene rearrangements and/or gene translocations and/or
  - \*Peptides containing one or more mutations and/or amino acid substitutions of the retinoblastoma protein and/or

\*Peptides containing one or more mutations and/or amino acid substitutions of proteins coded by oncogenes and/or protooncogenes and/or

\*Peptides containing one or more mutations and/or amino acid substitutions of proteins coded by anti-oncogenes and/or tumor suppressor genes and/or

\*Peptides derived from proteins differing in the target cell by one or amino acids from the proteins expressed by other cells in the same organism and/or

\*Peptides derived from viral antigens and/or coded by viral nucleic acids

The present invention also describes the combination of

I. Antisense nucleic acids, including ribozymes or derivatives thereof, transfected and/or directly applied as oligonucleotides or derivatives thereof capable of inhibiting expression and/or function of TGF- $\beta$ 1, TGF- $\beta$ 2, TGF- $\beta$ 3, IL-10 and/or PGE2-Receptor

with

## II. Vaccination with

- a) Chemokines, including lymphotactin and/or immune cell attracting and/or
- b) viruses and/or parts of viruses, including adenoviruses, papillomaviruses, Epstein-barr-Viruses, Viruses that are non-pathogenic including Newcastle-Disease virus, Cow-pox-virus and/or
- c) autologous and/or heterologous MHC-Molecules and/or
- d) molecules involved in antigen processing and/or
- e) molecules involved in antigen presentation and/or
- f) molecules involved in mediating immune cell effects and/or
- g) molecules involved in mediating immune cell cytotoxic effects and/or
- h) molecules involved in antigen transportation and/or
- i) co-stimulatory molecules
- j) peptides enhancing recognition by immune cell and/or cytotoxic effects of immune cells
- k) the peptides containing one or more amino acids differing between a protein in the target cell from the other cell within an organism

l) the peptides according to j) being

- \*Peptides containing one or more mutations and/or amino acid substitutions of the ras protein amino and/or

- \*Peptides containing one or more mutations and/or amino acid substitutions of the p53 protein and/or

- \*Peptides containing one or more mutations and/or amino acid substitutions of the EGF-Receptor protein and/or

- \*Peptides containing one or more mutations and/or amino acid substitutions of fusion peptides and/or fusion proteins and/or

- \*Peptides containing one or more mutations and/or amino acid substitutions and/or amino acid substitutions caused by gene rearrangements and/or gene translocations and/or

- \*Peptides containing one or more mutations and/or amino acid substitutions of the retinoblastoma protein and/or

- \*Peptides containing one or more mutations and/or amino acid substitutions of proteins coded by oncogenes and/or protooncogenes and/or

- \*Peptides containing one or more mutations and/or amino acid substitutions of proteins coded by anti-oncogenes and/or tumor suppressor genes and/or

- \*Peptides derived from proteins differing in the target cell by one or amino acids from the proteins expressed by other cells in the same organism and/or

- \*Peptides derived from viral antigens and/or coded by viral nucleic acids and/or

m) tumor cell extracts and/or tumor cell lysates and/or adjuvants.

The present invention also describes the combination of

I. Antisense nucleic acids, including ribozymes or derivatives thereof, transfected and/or directly applied as oligonucleotides or derivatives thereof capable of inhibiting expression and/or function of TGF- $\beta$ 1, TGF- $\beta$ 2, TGF- $\beta$ 3, IL-10 and/or PGE2-Receptor

with

II. Transfecting an organism containing target cells and/or target pathogens and/or transfecting the target cells and/or target pathogens with genes coding for

a) Chemokines, including lymphotactin and/or immune cell attracting and/or

b) viruses and/or parts of viruses, including adenoviruses, papillomaviruses, Epstein-barr-Viruses,

Viruses that are non-pathogenic including Newcastle-Disease virus, Cow-pox-virus and/or

c) autologous and/or heterologous MHC-Molecules and/or

d) molecules involved in antigen processing and/or

e) molecules involved in antigen presentation and/or

f) molecules involved in mediating immune cell effects and/or

g) molecules involved in mediating immune cell cytotoxic effects and/or

h) molecules involved in antigen transportation and/or

i) co-stimulatory molecules

j) peptides enhancing recognition by immune cell and/or cytotoxic effects of immune cells

k) the peptides containing one or more amino acids differing between a protein in the target cell from the other cell within an organism

l) the peptides according to j) being

\*Peptides containing one or more mutations and/or amino acid substitutions of the ras protein amino and/or

\*Peptides containing one or more mutations and/or amino acid substitutions of the p53 protein and/or

\*Peptides containing one or more mutations and/or amino acid substitutions of the EGF-Receptor protein and/or

\*Peptides containing one or more mutations and/or amino acid substitutions of fusion peptides and/or fusion proteins and/or

\*Peptides containing one or more mutations and/or amino acid substitutions and/or amino acid substitutions caused by gene rearrangements and/or gene translocations and/or

\*Peptides containing one or more mutations and/or amino acid substitutions of the retinoblastoma protein and/or

\*Peptides containing one or more mutations and/or amino acid substitutions of proteins coded by oncogenes and/or protooncogenes and/or

\*Peptides containing one or more mutations and/or amino acid substitutions of proteins coded by

anti-oncogenes and/or tumor suppressor genes and/or

\*Peptides derived from proteins differing in the target cell by one or amino acids from the proteins expressed by other cells in the same organism and/or

\*Peptides derived from viral antigens and/or coded by viral nucleic acids.

The present invention also describes the combination of

I. Antisense nucleic acids, including ribozymes or derivatives thereof, transfected and/or directly applied as oligonucleotides or derivatives thereof capable of inhibiting expression and/or function of TGF-B1, TGF-B2, TGF-B3, interleukin-10 (IL-10) and/or PGE2-Receptor

with

II. Applying to the organism containing target cells and/or target pathogens and/or to the target cells and/or target pathogens

a) Chemokines, including lymphotactin and/or immune cell attracting and/or

b) viruses and/or parts of viruses, including adenoviruses, papillomaviruses, Epstein-barr-Viruses, Viruses that are non-pathogenic including Newcastle-Disease virus, Cow-pox-virus and/or

c) autologous and/or heterologous MHC-Molecules and/or

d) molecules involved in antigen processing and/or

e) molecules involved in antigen presentation and/or

f) molecules involved in mediating immune cell effects and/or

g) molecules involved in mediating immune cell cytotoxic effects and/or

h) molecules involved in antigen transportation and/or

i) co-stimulatory molecules

j) peptides enhancing recognition by immune cell and/or cytotoxic effects of immune cells

k) the peptides containing one or more amino acids differing between a protein in the target cell from the other cell within an organism

l) the peptides according to j) being

\*Peptides containing one or more mutations and/or amino acid substitutions of the ras protein amino and/or

\*Peptides containing one or more mutations and/or amino acid substitutions of the p53 protein and/or

\*Peptides containing one or more mutations and/or amino acid substitutions of the EGF-Receptor protein and/or

\*Peptides containing one or more mutations and/or amino acid substitutions of fusion peptides and/or fusion proteins and/or

\*Peptides containing one or more mutations and/or amino acid substitutions and/or amino acid substitutions caused by gene rearrangements and/or gene translocations and/or

\*Peptides containing one or more mutations and/or amino acid substitutions of the retinoblastoma protein and/or

\*Peptides containing one or more mutations and/or amino acid substitutions of proteins coded by oncogenes and/or protooncogenes and/or

\*Peptides containing one or more mutations and/or amino acid substitutions of proteins coded by anti-oncogenes and/or tumor suppressor genes and/or

\*Peptides derived from proteins differing in the target cell by one or amino acids from the proteins expressed by other cells in the same organism and/or

\*Peptides derived from viral antigens and/or coded by viral nucleic acids and/or

m) tumor cell extracts and/or tumor cell lysates and/or adjuvants.

The present invention also describes a method for combining

- inhibition of immunosuppressive molecules including, but not limited to growth factors including, but not limited to Transforming growth factor beta (TGF- $\beta$ ) including the molecules TGF- $\beta$ 1, TGF- $\beta$ 2, TGF- $\beta$ 3, and/or Cytokines including, but not limited to Interleukin 10 (IL-10) and/or Prostaglandins, including prostaglandin E<sub>2</sub> (PGE<sub>2</sub>)

with

- stimulating or enhancing the immune response against diseased cells - such cells including tumor cells, cells infected by viruses or other pathogens cells of the immune system directed against autoantigens and/or cells involved in autoimmune diseases.

The present invention also describes a combination of molecules selected from

a) molecules interfering with the function or expression of immunosuppressive molecules including, but not limited to growth factors including, but not limited to Transforming growth factor beta (TGF-beta) including the molecules TGF- $\beta$ 1, TGF- $\beta$ 2, TGF- $\beta$ 3, and/or Cytokines including, but not limited to Interleukin 10 (IL-10) and/or Prostaglandins, including prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) and their receptors, including Transforming growth factor beta receptors, prostaglandin E<sub>2</sub> receptors and/or interleukin receptors including interleukin-10 receptors

and

b) molecules enhancing the immune response against diseased cells - such cells including tumor cells, cells infected by viruses or other pathogens cells of the immune system directed against autoantigens and/or cells involved in autoimmune diseases.

The present invention also describes

- Use of oligonucleotides including antisense oligonucleotides and/or use of antisense nucleic acids, including ribozymes or derivatives thereof, transfected and/or directly applied capable of inhibiting the function or expression of transforming growth factor beta (TGF- $\beta$ ) including the molecules TGF- $\beta$ 1, TGF- $\beta$ 2, TGF- $\beta$ 3, and/or of IL-10 and/or of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) receptors

in combination with

- use of methods and/or molecules enhancing the immune response against diseased cells or pathogens and/or methods and/or molecules enhancing immunogenicity of target cells and/or target pathogens and/or

- immunostimulatory molecules, including cytokines including interleukins including IL-1, IL-2, IL-12, IL-18, such cytokines being applied systemically to an organism including man or being applied locally e.g. to certain regions or organs or parts of organ or compartments of a body and/or

- enhancing expression of cytokines in target cells or pathogens by stimulating their expression and/or by transfecting expression systems into the target cell or target pathogen, capable of expressing these cytokines and/or

- chemokines attracting immune cells including lymphotactin, such chemokines being applied systemically to an organism including man or being applied locally e.g. to certain regions or organs or parts of organ or compartments of a body and/or

- enhancing expression of chemokines in target cells or pathogens by stimulating their expression and/or by transfecting expression systems into the target cell or target pathogen, capable of expressing these chemokines and/or

- peptides and/or antigens that are found in tumor cells and/or pathogens, but not in normal cells and/or

- enhancing expression of peptides and/or antigens that are found in tumor cells and/or pathogens, but not in normal cells and/or

- tumor cell extracts and/or tumor cell lysates and/or adjuvants.

## Claims

1. A method for stimulating the immune system comprising the steps of
  - a) inhibiting the synthesis and/or function of molecules suppressing and/or downregulating and/or negatively affecting the immune responsecombined with
  - b) enhancing the synthesis and/or function of molecules stimulating and/or enhancing and/or upregulating and/or positively regulating the immune response
2. The method according to claim 1, wherein the inhibition the synthesis and/or function of molecules suppressing and/or downregulating and/or negatively affecting the immune response is achieved using molecules inhibiting the synthesis or function of interleukin-10 and/or transforming growth factor beta and or Prostaglandin E<sub>2</sub> and/or receptors for Prostaglandin E<sub>2</sub>.
3. The method according to claims 1 or 2, wherein the enhancement of the synthesis and/or function of molecules stimulating the immune response is achieved by applying and/or enhancing the synthesis and/or function of interleukin-2 and/or interleukin-12 and/or interleukin-18 and/or viruses and/or viral antigens and/or antigens expressed in tumor cells and/or pathogens, but not in normal cells.
4. A combination of molecules obtainable according to the method according to any one of the claims 1 to 3.
5. A single molecule obtainable according to the method according to any one of the claims 1 to 3.
6. A nucleic acid molecule and/or a combination of nucleic acid molecules and/or chemical modifications and/or derivatives thereof obtainable according to the method according to any one of the claims 1 to 3
7. A composition comprising a molecule or combination of molecules according to claims 4 to 6 for the manufacturing of a medicament.
8. A medicament comprising an oligonucleotide according to any one of the claims 4 to 6 together with additives.
9. The use of molecules according to any of the claims claims 4 to 6 for the preparation of a medicament for the prevention or the treatment of neoplasm and/or infections.

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## A b s t r a c t

A method for stimulating the immune system comprising the steps of

a) inhibiting the synthesis and/or function of molecules suppressing and/or downregulating and/or negatively affecting the immune response

combined with

b) enhancing the synthesis and/or function of molecules stimulating and/or enhancing and/or upregulating and/or positively regulating the immune response